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REMARKS/ARGUMENTS

The claims remain as 1 and 8 and 10-14.

Claim 7 is amended to recite the excipient as suggested.

Claim 8 is similarly amended.

Claim Objectives

Reconsideration and withdrawal of the objection to Claim 7 is requested since the claim is now amended as suggested.

Claim Rejections – 35 U.S.C. § 112

Reconsideration and withdrawal of the rejection of Claims 8 and 10 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement, for the stated reasons that the claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, citing In *In re Wands*, 8 USPQ2d 1400 (1988).

Concerning the points itemized in the Wands decision, the following is stated.

1. The invention of Claim 10 relates to the use of imidazole characterized by among other features, the presence of a sulfonamide grouping, as a method of "preventing or treating a disease in a patent treatable with a pharmaceutical compound having hypoglycemic activity," the disease being one of those specified.

Claim 8 names the compound and simply itemizes its uses.

The invention is thus in the pharmaceutical field.

2. Concerning the state of the prior, this is continuing to seek advances in the treatment of the diseases named and pharmaceuticals containing a sulfonamide group (as glipizide and tolbutamide) or thiazolidenedione grouping are known as oral hypoglycemic

agents, please see the attached pages 1374 and 1375 of Remington, The Science and Practice of Pharmacy, Ed. , Gennard , 20th Ed – 2000.

The existence and effectiveness of hypoglycemic agents is therefore well established.

3. Concerning the matter of predictability in this art, the following is offered.

The U.S. Patent Office has allowed U.S. Patent 6,242,474 over which the subject application has been rejected for double patenting, which contains in its Claim 9 the following:

> 9. A method for preventing or treating impaired glucose tolerance, diabetes, diabetic complications, syndrome of insulin resistance, polycystic ovary syndrome, hyperlipidemia, atherosclerosis, cardiovascular disorders, hyperglycemia, and hypertension comprising administering to a patient in need thereof an effective amount of a heterocyclic aromatic ring compound represented by formula (I):

wherein formula (I) is a generic formula.

Clearly, sufficient predictability has been recognized by the U.S. Patent Office.

Please also note that in Claim 10, all the diseases recitations are limited to versions "treatable with a pharmaceutical compound having hypoglycemic activity."

The following establishes that treatment predictability in regard to such diseases exists. Copies of the citations are attached.

J.A. Cornicelli, Atherosclerosis, 1997, 2(2), 43-49

This publication is entitled "Diabetes, Insulin Resistance, Hyperinsulinemia and Vascular Disease: A Therapeutic Challenge for the 90s".

This publication teaches that Troglitazone (please see the Remington text, pg. 1375), which lowers the blood sugar level, may be important for preventing the onset of diabetes in obese individuals with impaired glucose tolerance (page 46, right column, lines 8-11). In Applicants' view, the compound of the present invention which lowers blood sugar level is easily expected to be effective for the prevention of diabetic complications, insulin resistance

syndrome etc. from the teachings of this publication. This publication also discloses that Troglitazone is effective for hypertriglyceridemia and hypertension (page 45, column 2, the central paragraph penultimate sentences).

Endocr Pract, 2001, 7(4), 279-86

This publication teaches that Troglitazone will be effective for polycystic ovary syndrome. The Abstract is submitted.

Arterioscler Thromb. Vasc. Biol., 2001, 21(12), 1891-5.

This publication teaches that TZDs (thiazolidene diones) improve cardiovascular risk factor and delays the atherosclerotic process. (The Abstract is submitted).

Arch Dermatol, 2000, 136(5), 609-16

This publication teaches that Troglitazone is effective for psoriasis, i.e., one of the skin disorders related to an anomaly of differentiation of epidermic cells. (Abstract submitted).

Endocrinolgy, 1999, 140(11), 5060-5

This publication teaches that thiazolidinedione derivatives having an antidiabetic activity are effective for inhibition of bone resorption. Therefore, it is easily expected that these derivatives will be effective for osteoporosis. (Abstract submitted).

U.S. 6,353,009

This USP teaches that an insulin sensitivity enhancer has an ability to treaty and/or prevent hyperuriucemia.

Kirk-Othmer Encyclopedia of Chemical Technology, 4th Ed., 1995, page 675 states that Diazoxide exhibits hypoglycemic and antihypertensive effects.

Please note the following quotations:

> A body of evidence is accumulating relating hyperinsulinemia, insulin resistance and vascular disease (Cornicelli, page 43, column 1, penultimate sentence in the first paragraph).

The action of this compound (troglitozone) may also be important in preventing the onset of diabetes in obese individuals with impaired glucose tolerance (Cornicelli, page 46, column 1, sentence at line 8).

Cornicelli states, referring to troglitazone/a thizide)

[64]. Treatment with this agent completely prevented the development of insulin resistance, hypertension and hypertriglyceridemia in fructose-fed rats [65]. (Cornicelli, page 45, penultimate sentence in next to last paragraph).

Current evidence suggests that the use of insulin-sensitizing agents in patients with polycystic ovary syndrome not only improves their sensitivity to the effects of insulin on glucose and lipid metabolism but also ameliorates clinical and biochemical manifestations of hyperandrogenism and increases rates of ovulation. (Endoc. Pract. 2001, 7(4), 279-86), Abstract, penultimate sentence.

Thiazolidinediones (TZDs) are oral insulin sensitizers in broad clinical use that enhance insulin-stimulated glucose uptake into skeletal muscle. TZDs can also improve cardiovascular risk factors and exert direct effects on vascular cells to potentially retard the atherosclerotic process. (Arterioscler Thromb. Vasc. Biol., 2001, 3rd and 4th sentences of Abstract)

All patients' psoriasis improved substantially during troglitazone therapy. (Arch Dermatol. 2000, below center of Abstract stating results of a test on normoglycemic patients.)

Thus, TZDs may suppress bone resorption in diabetic patients and prevent bone loss. (Endocrinology, 199, last sentence of Abstract).

Claim 1 of USP 6,353,009, reads as follows:

1. A method for the treatment or prevention of hyperuricemia in a human in need thereof, which comprises administering to said human an amount of insulin sensitivity enhancer effective to reduce or prevent hyperuricemia.

The Kirk-Othmer citation includes the following (page 675, last paragraph, first sentence)

Diazoxide [364-98-7] (3-methyl-7-chloro-1,2,4-benzothiadiazine, 1,1-dioxide) is a nondiuretic thiazide used for its

hyperglycemic actions when given orally (Proglycem) and for its antihypertensive effects when given intravenously (Hyperstat IV.)

3. The predictability or lack thereof in the art.

Based upon the above literature citations, it would appear that sufficient predictability exists to sustain Applicants' claims.

4. The amount of direction or guidance present

For pharmaceutical applications, it would appear that the disclosure (page 21, paragraph at line 5) of preparation types for therapeutic administration as well as dosage is of the nature that has been accepted as sufficient in the past.

5. The presence or absence of working examples.

The application is replete with Examples for preparing the compounds. The blood sugar level depressing activity in mice, is demonstrated in Experimental Ex. 1, pages 19-21 for a representative compound, that of Example 11.

6. The breadth of the claims

The claims are limited in the sense that they specify the compound as one requiring the presence of a sulfonamide group and a diazide group, substituted as specified, and linked as specified through a defined linking group L.

The diseases that are treatable are listed and all qualified by "in a patient treatable with a compound having hypoglycemic activity", in the method Claim 10.

Claim 8 (the composition recited as a preparation), merely limits the preparation as one used for the recited purpose.

7. The quantity of experimentation needed

The various citations submitted established that the quantity of experimentation needed is known and acceptable in this art.

8. The level of skill in the art

This is obviously very high.

In view of the above, it would appear that the criteria set forth in the In re Wands decision have been satisfied.

All the diseases recited in the method Claim 10 are limited by the common thread "disease in a patient treatable with a pharmaceutical compound having hypoglycemic activity".

As for the composition Claim 8, this simplify lists possible uses. The composition is infringed by a non-authorized sale whether or not so used.

Favorable reconsideration is therefore solicited of the stated rejection.

Reconsideration and withdrawal of the rejection of Claims 2, 3 and 5 under 35 U.S.C. §112, second paragraph for the stated reasons are requested.

The Official Action, page 8, states:

> Claim 2 does not further limit claim 1 {see definition (10) under variable R^6}. Compounds 30 and 31 in claim 5 are not embraced by claim 1 (see the R^1 definition and the possible substituents).

In support of that conclusion, the Official Action states, page 10,

> Nothing in the original filed claims or the instant specification would lead, suggest, or teach to one skilled in the art to substitute any of the claimed substituents of definitions (1)-(11), under R1 in claim 1, on the "alkyl" portion of the "alkylaryl" (which is embraced by the definition of "aryl") instead of the aryl portion of the "alkylaryl").

In response, Applicants point out that formula IA of Claim 2, which also appears on page 11 of the specification serves in fact, among other purposes, as a disclosure of just such substitution of claimed substituents under R^1 on the alkyl portion of the "alkylaryl" embraced by disclosed definition of "aryl".

In formula (IA) unsubstituted aryl appears as the benzene ring in the depicted phenyl (radical substituted by chlorine (halogen)) at the ortho position. Since only o-chloro aryl(phenyl) is specifically depicted in formula (IA), substituents identified by R^6 must be

separately named. They are indeed so separately named as in recitations (4), which names "halo(lower)alkyl", and (10), which names "lower alkyl optionally substituted by aryloxy".

Compounds 30 and 31 of Claim 5 are within the scope of Claim 2 and therefore within the scope of Claim 1.

All that is involved is a change in terminology, with no change in substance.

Formula (IA) thus specifically names the substituents in question, "halo" in substituent (4) and "aryloxy" in substituent (10) on the alkyl portion of "alkyl substituted aryl" included by definition within the term "aryl". This appears also clearly in Preparation 27-1, page 43 where the grouping "-4-[phenoxymethyl]benzene" appears.

Concerning the quotations from the specification, bridging pages 9 and 10 of the Official Action, those portions of the specification relate to exemplification of "alkyl" per se. Substitution is dealt with elsewhere, as in the paragraph bridging pages 5 and 6 and quite generally in the following quotation at page 11, line 18.

> When the above-mentioned substituents are substituted, the number of the substituents is preferably 1 to 4, unless particularly specified.

The above is immediately followed by formula (IA).

In principle, Applicants' position is exemplified by reference to nomenclature relating to substitution on toluene.

(1) (chloromethyl)benzene and (2) α-chlorotoluene are the same compounds and (3) benzyl chloride is a third name.

The first name is used when the benzene portion of the aromatic compound toluene is written out, as in Claim 2 and Preparation Example 27-1. The second name is suitable where the bezene ring is implied by the generic terminology , as in Claim 1. The third is suitable when the C_6H_5-CH_2- grouping is to be identified.

Accordingly, compounds subgenerically named as in Claims 2 and 3, and specifically named, as in Claim 5, are within the scope of Claim 1 and limit it as applied to e.g., compound (30) in Claim 5. Another less elegant name for the grouping in issue is α-phenoxy-p-tolylmethyl-.

In summary, it is Applicants' position

(1) that examples of substitution of the alkyl group on an alkyl substituted aryl moiety (within the disclosed broad definition of aryl) are disclosed.

(2) that Claims 2, 3 and 5 are within the scope of Claim 1.

Claim 3 would appear to be free of the stated criticism.

It is added that Applicants should not be faulted for precisely defining what they intend by "aryl". Their definition conforms to that which is standard in the chemical art, note the definition of "aryl" in Webster's Third New International Dictionary 1993, pg. 125).

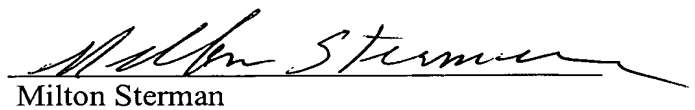
> ar-yl 1: a univalent aromatic radical (as phenyl or tolyl) derived from an arene by removal of one hydrogen atom from a carbon atom of the nucleus-

The consultant for Chemistry was Patterson, former editor of Chemical Abstract.

Favorable reconsideration is solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.
Norman F. Oblon



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20 TH EDITION

Remington: The Science and Practice of Pharmacy

ALFONSO R GENNARO
Chairman of the Editorial Board
and Editor

Table 77-5. Oral Hypoglycemic Agents

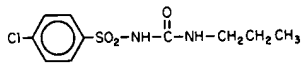
DRUG	COMMENTS
First-generation sulfonylureas	
Tolbutamide	Short acting (6–12 hr)
Tolazamide	Similar to tolbutamide; intermediate acting (10–14 hr); has active metabolites
Acetohexamide	Similar to tolbutamide; intermediate acting (12–24 hr); has active metabolite
Chlorpropamide	Long acting (up to 60 hr); ADH-like action, more serious toxicities
Second-generation sulfonylureas	
Glyburide	More potent than first-generation drugs; effects persist for 24 hr
Glipizide	Shorter half-life (2–4 hr); available as extended-release preparation
Glimepiride	Similar to glyburide and glipizide; more potent; longer half-life (5 hr)
Biguanides	
Metformin	Actions do not involve stimulation of insulin secretion, some GI effects; rarely lactic acidosis
Meglitinides	
Repaglinide	Similar in action to sulfonylureas; short acting (half-life = 1 hr)
Thiazolidinediones (Glitazones)	
Troglitazone	Decreases insulin resistance by effects on target organs
Rosiglitazone	Similar to troglitazone
Pioglitazone	Similar to troglitazone

diated by a competitive, reversible inhibition of pancreatic α-amylase membrane-bound intestinal α-glucosidase hydrolase enzymes. Acarbose is metabolized exclusively within the GI tract, principally by intestinal bacteria but also by digestive enzymes. The small fraction of active drug that is absorbed is excreted completely by the kidneys.

The most commonly observed side effects are mild-to-moderate GI effects such as flatulence (77%), diarrhea (33%), and abdominal discomfort (21%) that generally diminish in frequency and intensity with time.

CHLORPROPAMIDE

Benzenesulfonamide, 4-chloro-*N*-[(propylamino)carbonyl]-, Diabinese



1-[(*p*-Chlorophenyl)sulfonyl]-3-propylurea [94-20-2] $C_{10}H_{13}Cl\text{-}N_2O_3S$ (276.74).

Preparation—*p*-Chlorobenzenesulfonamide undergoes addition to propyl isocyanate by warming a solution of equimolar quantities of the two reactants.

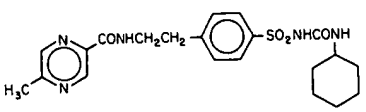
Description—White, crystalline powder, with a slight odor; melts between 125° and 129°.

Solubility—Practically insoluble in water; soluble in alcohol; sparingly soluble in chloroform.

Comments—An oral hypoglycemic agent with actions and uses essentially the same as those of *Tolbutamide*. As with tolbutamide, its use is limited to patients with stable, mild to moderately severe diabetes mellitus who still have some residual pancreatic β-cell function. Refractoriness sometimes develops. Elimination is about 80% hepatic. The half-life (25 to 60 hr) and duration of action (about 24 to 48 hr) are much longer than those of tolbutamide. The side effects are of the same type as with tolbutamide but have a somewhat higher incidence, namely, about 6%, half of which are cutaneous. It increases the endogenous release of vasopressin (ADH) and thus causes water retention with resultant hyponatremia and hypo-osmolality. This action is used in the treatment of central diabetes insipidus. Patients under treatment with this drug have a disulfiram-like intolerance to alcohol. It is contraindicated in the presence of renal glycosuria because of the possibility of fatal hypoglycemia.

GLIPIZIDE

Pyrazinecarboxamide, *N*-[2-[4-[[[(cyclohexylamino)carbonyl]amino]sulfonyl]phenyl]ethyl]-5-methyl-, Glucotrol



[29094-61-9] $C_{21}H_{27}N_5O_4S$ (445.54).

Preparation—By the condensation of 4-[2-(5-methyl-2-pyrazinecarboxamido)ethyl]benzenesulfonamide and cyclohexyl isocyanate; *Arzneimittel-Forsch* 1971; 21:200.

Description—White, odorless powder; pK_a 5.9; melts about 205°.

Solubility—Insoluble in water or polar solvents; freely soluble in dimethylformamide or fixed alkalies.

Comments—A sulfonylurea used to treat Type 2 diabetes mellitus that is 100 times more potent than tolbutamide in evoking pancreatic secretion of insulin. It differs from other oral hypoglycemic drugs in that tolerance to this action apparently does not occur. It also upregulates insulin receptors in the periphery, which seems to be the primary action. It is thought not to have a direct effect on glucagon secretion. It is mildly diuretic. It has a special status in the treatment of non-insulin-dependent diabetes mellitus because it is effective in many patients who are resistant to all other oral hypoglycemic drugs. It differs from other oral hypoglycemic drugs in that it is more effective during eating than during fasting.

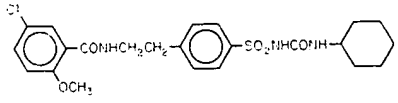
Adverse effects have been reported to occur in as few as 3% and as many as 12%. GI effects, such as nausea, heartburn, diarrhea, constipation, vomiting, and colic, are the most common and occur with a frequency of 1.7 to 3.7%. Rashes occur in 0.5 to 1.5%. Mild headache, drowsiness, asthenia, and dizziness occasionally occur. Minor episodes of hypoglycemia can occur.

Peroral absorption is almost complete. It is rapid (about 30 min) if the stomach is empty, but 1.2 to 3.5 hr is required in the presence of food.

About 98% is bound to plasma albumin by nonionic forces. The volume of distribution is about 0.16 L/kg. About 90% is metabolized in the liver to several inactive metabolites. The half-life is about 2 to 4 hr. The duration of action is 10 to 16 hr.

GLYBURIDE

Benzamide, 5-chloro-*N*-[2-[4-[[[(cyclohexylamino)carbonyl]amino]sulfonyl]phenyl]ethyl]-2-methoxy-, DiaBeta; Glynase Pres Tab; Micronase



Glybenclamide [10238-21-8] $C_{23}H_{28}ClN_3S$ (494.00).

Preparation—See *Arzneimittel-Forsch* 1966; 16:640; *CA* 66:65289h.

Description—White to off-white crystalline powder; melts about 170°; pK_a 5.3.

Solubility—Sparingly soluble in water or ether; 1 g dissolves in 330 mL of alcohol or 36 mL of chloroform.

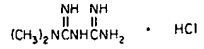
Comments—A sulfonylurea hypoglycemic drug used for Type 2 diabetes mellitus. It is 200 times as potent as tolbutamide in evoking the release of insulin from the pancreatic islets. It is more effective in suppressing fasting than postprandial hyperglycemia. Like glipizide, it is mildly diuretic.

The incidence of adverse effects is reported to be 3.6%. GI side effects, such as nausea, anorexia, vomiting, heartburn, diarrhea, constipation, and abdominal pain, occur with a frequency of about 2%. Pruritus and rashes may occur. Cholestatic jaundice and eosinophilia have been reported. Transient leukopenia sometimes occurs. A disulfiram-like reaction to alcohol may occur. Hypoglycemic episodes sometimes are prolonged and severe, and deaths have resulted.

About 90% of oral drug is absorbed from an empty stomach. The absorption time is 1.5 to 2 hr. Food decreases absorption, some fibers decreasing it by as much as 50%. About 97% is bound to plasma albumin as a weak-acid anion and, hence, is susceptible to displacement by many weak acid drugs. Elimination is by hepatic metabolism. The half-life is 1.5 to 5 hr. The duration of action is 24 hr. The micronized tablets are not strictly bioequivalent to nonmicronized tablets in their onset of action or half-life.

METFORMIN HYDROCHLORIDE

Imidodicarbonimidic diamide, *N,N*-dimethyl-, monohydrochloride; Glucophage; Metiguanide



[657-24-9] $C_4H_{11}N_5.HCl$(165.67).

Preparation—By the reaction of dimethylamine hydrochloride with dicyandiamide to yield the base; *J Am Chem Soc* 1959; 81: 2220, 3728.

Description—White crystals melting about 230°

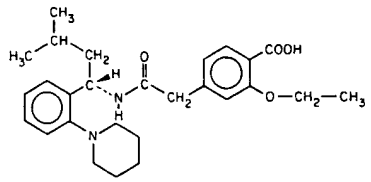
Solubility—Soluble in water or alcohol; practically insoluble in ether or chloroform.

Comments—An oral antihyperglycemic drug used in the management of Type 2 diabetes mellitus. It may be used as monotherapy or as an adjunct to diet or a sulfonylurea to lower blood glucose levels. It improves glucose tolerance by lowering both basal and postprandial glucose. Its mechanism of action is distinct from that of sulfonylureas and does not result in hypoglycemia. It decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Oral bioavailability under fasting conditions is 50 to 60%, and food decreases the extent of absorption. The drug is excreted unchanged in the urine and does not undergo hepatic metabolism.

Adverse effects are primarily GI symptoms such as diarrhea, nausea, vomiting, abdominal bloating, flatulence, and anorexia. A rare but serious toxicity that can occur with metformin is lactic acidosis.

REPAGLINIDE

***p*-Toluic acid, (+)-2-ethoxy-α-[[(*S*)-α-isobutyl-*o*-piperidinobenzyl]carbamoyl]-, Prandin**



[135062-02-1] $C_{27}H_{36}N_2O_4$ (452.59).

Preparation—See Int Pat Appl WO 93 00,337 (1993).

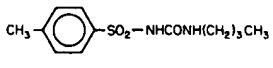
Description—White powder melting about 129°.

Comments—An oral hypoglycemic agent that is a meglitinide (the nonsulfonylurea moiety of glyburide) that is used in the management of Type 2 diabetes mellitus. It acts by stimulating insulin secretion by binding to and inhibiting the ATP-dependent potassium channels in the β-cell membrane, resulting in an opening of calcium channels. It is absorbed rapidly and completely from the GI tract and is completely metabolized in the liver by oxidative biotransformation and direct glucuronidation. It has a short half-life in the bloodstream of 1 hr. The hepatic cytochrome P-450 system 3A4 is involved in the metabolism of repaglinide, which may be inhibited by some drugs including ketoconazole, miconazole, and erythromycin.

The most common adverse effect is hypoglycemia. The incidence of serious cardiovascular events (3 to 4%) is similar to that with glyburide and glipizide in comparative trials.

TOLBUTAMIDE

Benzenesulfonamide, *N*-[(butylamino)carbonyl]-4-methyl-, Orinase



1-Butyl-3-(*p*-tolylsulfonyl)urea [64-77-7] $C_{12}H_{18}N_2O_3S$ (270.35).

Preparation—Toluene is treated with chlorosulfonic acid and the resulting *p*-toluenesulfonyl chloride is converted into *p*-toluenesulfonamide by interaction with ammonia. Condensation of the sulfonamide with ethyl chloroformate in the presence of pyridine or another suitable basic catalyst produces ethyl *N*-*p*-toluenesulfonylcarbamate. Aminolysis with butylamine in ethylene glycol monomethyl ether solutions yields tolbutamide.

Description—White, or practically white, crystalline powder; slightly bitter and practically odorless; melting range is 126 to 132°.

Solubility—Practically insoluble in water, soluble in alcohol or chloroform.

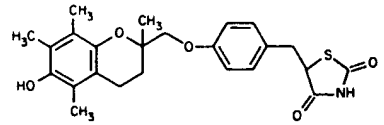
Comments—An oral hypoglycemic drug. It is useful in the treatment of selected cases of non-insulin-dependent diabetes mellitus. To respond, patients must have some remaining functional islet β-cells that can be stimulated by the drug. Patients who require more than 40 Units of insulin/day generally will not respond to this drug. In diabetic patients the peak effect is reached in 5 to 8 hr. The duration of action is usually 6 to 12 hr (average plasma half-life, 5.6 hr but longer in elderly patients; dose-dependent kinetics occur with high doses), so that two daily doses are required in most patients. The hypoglycemia induced by even high doses of the drug is generally not as severe as can be induced by insulin; hence, the incidence of acute hypoglycemic reactions is lower with tolbutamide; however, severe, refractory hypoglycemia sometimes does occur. Refractoriness to it sometimes develops.

Toxic effects include diarrhea, nausea, vomiting, abdominal cramps, weakness, headache, tinnitus, paresthesias, allergic reactions (pruritus, erythema multiforme, maculopapular rash, all usually transient), photosensitivity, and alcohol intolerance. Water retention and hyponatremia may result from enhancement of ADH (vasopressin) release. Cholestatic jaundice may occur (rarely), and the drug is contraindicated in the presence of liver damage. Rare leukopenia, thrombocytopenia, pancytopenia, and agranulocytosis occur. Hypoglycemic reactions are rare. It is contraindicated in nondiabetic patients with renal glycosuria and liver disease.

The sulfonylureas interact with a number of drugs. The following substances increase the hypoglycemic activity of sulfonylureas: dicumarol, phenylbutazone, oxyphenbutazone, several sulfonamides, chloramphenicol, large doses of salicylates, monoamine oxidase inhibitors (MAOIs), clofibrate, anabolic steroids, fenfluramine, guanethidine, β-adrenoreceptor-blocking drugs, and alcohol.

TROGLITAZONE

2,4-Thiazolidinedione, (±)-5-[[4-[3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-yl)methoxy]phenyl]methyl]-, Rezulin



[97322-87-7] $C_{24}H_{27}NO_3S$ (441.55).

Preparation—See US 4,572,912 (1985).

Description—White to yellowish with faint characteristic odor, melting about 185°.

Solubility—Soluble in DMF, anhydrous ethanol, acetonitrile, or ether; practically insoluble in water.

Comments—An oral drug that improves the responsiveness to insulin, when patients with Type 2 diabetes mellitus have problems of insulin resistance, by a unique mechanism of action compared with those of other drugs available. It is currently only approved for use with insulin. The drug decreases blood glucose in diabetic patients with hyperglycemia by improving target organ response to insulin. In the presence of exogenous or endogenous insulin, the drug decreases hepatic glucose output, increases insulin-dependent glucose uptake and use by skeletal muscle, and increases glucose uptake and decreases fatty acid output in adipose tissue. Troglitazone binds to nuclear receptors called peroxisome proliferator-activated receptors (PPARs) that regulate transcription of a number of insulin-responsive genes critical to glucose and lipid metabolism. It is not an insulin secretagogue.

It is absorbed rapidly upon oral administration, and food increases the extent of absorption by 30 to 80%; therefore, it is taken with meals to enhance systemic availability. The drug is highly bound (>99%) to serum albumin. It is metabolized in the liver to several inactive compounds including a sulfate conjugate, the major metabolite, and primarily eliminated in the feces. The hepatic cytochrome P-450 that is involved in metabolism is CYP3A4, so drug interactions can be expected when used in combination with drugs such as oral contraceptives, terfenadine, and others that are metabolized by the same enzyme.

The incidence of side effects is relatively low, including headache and respiratory infections. It is important to monitor liver function by measuring increases in serum levels of aminotransferases that occur in 1 to 2% of patients. In addition, serious hepatotoxicity may occur in rare

Webster's Third New International Dictionary

OF THE ENGLISH LANGUAGE UNABRIDGED

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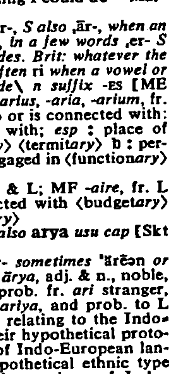
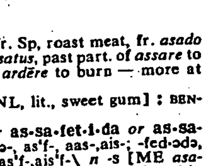
artist lithography *n* : AUTOLITHOGRAPHY
art·ist·ry \'ärd·əstrē, 'äl, |tə-, -ri\ *n* -ES **1** : artistic quality of effect or workmanship ⟨the ~ of this first chapter —G.H. Genzmer⟩ **2** : artistic ability ⟨to be on the winning side in every argument requires an ~ not always fully appreciated —Julian Dana⟩
artist's proof *n* : one of the first and therefore best proofs printed from an engraved plate
art·less \'ärtləs, 'ät-\ *adj* **1 a** : lacking art, skill, or knowledge : IGNORANT, UNSKILLFUL ⟨to be ~ is to be dehumanized —E.A. Hoebel⟩ **b** : devoid of artistic quality or taste : UNCULTURED ⟨the land vaguely realizing westward but still unstoried, ~ —Robert Frost⟩ **2** : free from the artificial : easy, natural, and not contrived ⟨its atmosphere of something we call an ~ charm pervades through the narrative —H.V.Gregory⟩ **3** : made or contrived without skill or art : CRUDE, INARTISTIC ⟨marred by an ~ summerhouse in the garden⟩ **4** : marked by freedom from calculated craft, guile, and duplicity and by sincerity, simplicity, and genuineness ⟨open, candid, ~, guileless, with affections strong, but simple, forming no pretensions, and knowing no disguise —Jane Austen⟩ **syn** see NATURAL
art·less·ly *adv* : in an artless manner : without art, skill, or guile : UNAFFECTEDLY
art·less·ness *n* -ES : the quality or state of being artless
art marble *n* : a cast stone made of crushed marble with the exposed surface highly polished to resemble natural marble
art music *n* : music composed by the trained musician as contrasted with folk music and often with popular music
art nou·veau \,är,nü'vō\ *n, often cap A&N* [F, lit., new art] : a late 19th century and early 20th century decorative style characterized by organic foliate forms, sinuous lines, and nongeometric curves
arto- *comb form* [L, fr. Gk, fr. *artos*; perh. akin to Gk *ararískein* to fit — more at ARM] : bread ⟨*Artocarpus*⟩
art object *n* [by trans.] : OBJET D'ART
ar·to·car·pus \,ärd·ə'kärpəs\ *n* [NL, fr. *arto-* + *-carpus*] **1** *cap* : a large genus of tall evergreen milky-juiced trees (family Moraceae) orig. Asiatic but now grown throughout the tropics having large alternate entire or lobed leaves and flowers in catkinlike clusters with the pistillate ones in crowded heads that produce a multiple fleshy fruit **2** -ES : a plant of the genus *Artocarpus* : BREADFRUIT, JACKFRUIT
art of self-defense 1 : BOXING **2** : FENCING
art·o·gra·vure \,ärd·əgrə'vyů(ə)r\ *n* -S [²*art* + *-o-* + *gravure*] : the process of preparing silk-screen stencils photographically by sensitizing the silk and printing the image on it
ar·to·pho·ri·on \-'fōrē,än\ *n, pl* **artopho·ria** \-rē,ə\ [MGk, fr. Gk, bread basket, fr. *arto-* + *-phorion* (akin to *pherein* to carry) — more at BEAR] : a container for the reserved sacrament in the Eastern Church
ar·to·type \'ärd·ə,tīp\ *n* -S [²*art* + *-o-* + *type*] : COLLOTYPE
ar·to·ty·rite \,ärd·ə'tī,rīt\ *n* -S *usu cap* [LL *Artotyrita*, fr. LGk *Artotyritēs*, fr. Gk *artotyros* bread and cheese (fr. *arto-* + *tyros* cheese) + *-itēs* -ite — more at TYR-] : one of a Montanist sect that according to its opponents used bread and cheese in the celebration of the Lord's Supper
art paper *n* **1** *Brit* : coated paper **2** : heavy colored paper used esp. by students for art or craft projects — compare CONSTRUCTION PAPER
arts *pl of* ART
-arts *pl of* -ART
arts and crafts *n pl* : the arts of decorative design and handicraft (as bookbinding, weaving, and needlework) that are concerned with objects of use
arts college *n* : a college in which the liberal arts are the only or the principal studies
artsman *n, pl* **artsmen** *obs* : a man skilled in an art
arts master *n, obs* : a teacher or master of art or of an art
art song *n* : a song that is lyric in character with melody and accompaniment usu. through-composed by a trained musician — see LIED; compare FOLK SONG
art square *n* : a patterned rectangle of carpet woven in one piece for a rug
art theater *n* : a theater that specializes in the presentation of artistic dramatic productions and esp. foreign films
art union *n* : any of several 19th century American associations for promoting the arts esp. through the distribution of paintings and prints by lottery
artware \'=,=\ *n* : merchandise (as knickknacks) that is aesthetic as well as utilitarian
artwork \'=,=\ *n* **1 a** : the making of decorative or artistic objects by hand **b** : the decoration of artistic objects so made **2** : artistic work produced in quantity; *specif* : 19th century factory-made objects **3** : ART 8
arty \'ärd·ē, 'äl, |tē, -i\ *adj* -ER/-EST **1** : imitative often unsuccessfully of art : having some of the showier characteristics of art ⟨no ~ or pretentious line ever got into his daily cartoon —James Thurber⟩ **2** : aspiring often unsuccessfully to be artistic : showing dilettante interests : marked by concern with accidental rather than essential characteristics of art ⟨his ~ but beautiful wife —V.P.Hass⟩
arty *abbr* artillery
arty-crafty \¦=¦=¦=\ *also* **arty-and-crafty** \¦===¦==\ *or* **artsy-craftsy** \¦ärtsē¦kraf(t)sē\ *adj* [irreg. fr. *arts and crafts*] **1 a** : simultaneously arty and somewhat useless, novel, and often expensive and uncomfortable ⟨*arty-crafty* lawn furniture⟩ **b** : marked by pretension esp. to artlessness or simplicity ⟨*arty-crafty* street terminology that garden suburbs have lately made their own —*Architectural Rev.*⟩ **2** : ARTY 2 ⟨a free-thinking, *arty-crafty* little sculptress —Eleazar Lipsky⟩
arua \,ärə¦wä\ *n, pl* **arua** *or* **aruas** *usu cap* [Pg *aruá*, of Amer Ind origin] **1 a** : an Arawakan people of French Guiana and Brazil **b** : a member of such people **2** : the language of the Arua people
aruac *usu cap, var of* ARHUACO
arui \'ärü,ē\ *n* -S [native name in eastern Africa] : AOUDAD
aru·ke \'ärü,kā\ *n* -S [Maori *aruhe*] *New Zeal* : the starchy rhizome of the brake (*Pteridium aquilinum*)
ar·um \'a(a)rəm, 'er-, 'är-\ *n* [NL, fr. L, arum, fr. Gk *aron*; perh. akin to L *arundo* reed] **1** *cap* : a genus (the type of the family Araceae) of herbs of Europe and Asia with usu. heart-shaped leaves and a large spathe with edges involute at the base **2** -S : any of several plants of the family Araceae, esp. of the genus *Arum* — see CUCKOOPINT **3** -S : a sagolike starch obtained from cuckoopint root : PORTLAND ARROWROOT
arum family *n* : ARACEAE
arum lily *n* : CALLA LILY
arun·cus \ə'rəŋkəs\ *n, cap* [NL, fr. L, beard of a goat, fr. (assumed) Gk (Dor) *aryngos*; akin to Gk (Attic) *ēryngos*] : a small genus of herbs (family Rosaceae) found in No. America and Japan and having compound leaves and a showy branched cluster of white flowers — see GOATSBEARD
arun·del \ə'rənd^əl\ *adj, usu cap* [fr. Anne Arundel county, Md.] : of or relating to a subdivision of the Lower Cretaceous
arun·di·na·ceous \ə¦rəndə¦nāshəs\ *adj* [L *arundinaceus*, *harundinaceus* reedlike, fr. *arundin-*, *arundo*, *harundin-*, *harundo* reed + *-aceus* -aceous] : of or relating to a reed : resembling reed or cane
arun·di·nar·ia \ə,rəndə'na(a)rēə\ *n, cap* [NL, fr. L *arundin-*, *arundo*, *harundin-*, *harundo* reed + NL *-aria*] : a genus of large woody bamboo grasses that are natives of Asia and America and have terete culms, persistent leaf sheaths with stiff scabrous bristles, and flower spikelets arranged in racemes or panicles — compare CANEBRAKE, GIANT CANE, SMALL CANE
arun·do \ə'rən(,)dō\ *n, cap* [NL, fr. L *arundo*, *harundo* reed] : a small genus of coarse tall grasses found in most

aruspex *var of* HARUSPEX
arv *abbr* arrive
¹**ar·val** *also* **ar·vel** \'ärvəl\ *n* -S [ME *arvell*, of Scand origin; akin to ON *erfiöl* funeral feast, fr. *erfi* inheritance, funeral feast + *öl* ale, drinking bout, banquet; akin to ON *arfi* inheritance — more at ORPHAN, ALE] *dial Brit* : a funeral feast
²**arval** \"\ *adj, usu cap* [L *arvalis*, lit., of cultivated field, fr. *arvum* cultivated field + *-alis* -al] : relating to a body of ancient Roman priests who presided over an annual fertility festival in May
ar·ver·ni \är'vər,nī\ *n pl, usu cap* [L] : a powerful and civilized people of southern Gaul that were conquered by Caesar in his Gallic wars
¹**ar·vic·o·la** \-'vikələ\ *n, cap* [NL, fr. LL *arvi-* (fr. L *arvum* cultivated field, fr. neut. of *arvus* arable) + L *-cola* inhabitant; akin to L *arare* to plow — more at EAR, -COLOUS] : a genus of rodents consisting of the water voles
²**arvicola** \"\ [NL, fr. LL *arvi-* + L *-cola*] *syn of* MICROTUS
ar·vi·cole \'ärvə,kōl\ *n* -S [NL *Arvicola*] : a member of the genus *Arvicola*
ar·vi·cul·ture \-,kəlchər *also* ,==¦==\ *n* -S [prob. fr. F, fr. LL *arvi-* + F *culture*] : the cultivation of field crops : the science and art of growing field crops
ARW *abbr* air raid warden
ary \'arē, 'er-, 'aar-, -ri *S also* 'ar *or* 'aə\ *adj* [alter. of *e'er a*, fr. *e'er* + ²*a*] *dial* : ANY, A ⟨was there ~ thing I could do —Marjorie K. Rawlings⟩
¹**-ary** *US*: ,erē, ,eri, *infrequently* ,ər- *or* r-, *S also* ,är-, *when an unstressed syllable precedes*: ,ər- *also* r-, *in a few words* ,er- *S also* ,är-, *when a stressed syllable precedes. Brit: whatever the preceding stress, usu* ,əri, *alternatively often* ri *when a vowel or semivowel does not immediately precede*\ *n suffix* -ES [ME *-arie*, fr. OF & L; OF *-arie*, *-aire*, fr. L *-arius*, *-aria*, *-arium*, fr. *-arius*, adj. suffix] : one that belongs to or is connected with: *esp* : place of **a** : thing belonging to or connected with; *esp* : place of ⟨avi*ary*⟩ ⟨besti*ary*⟩ ⟨herb*ary*⟩ ⟨semin*ary*⟩ ⟨termit*ary*⟩ **b** : person belonging to, connected with, or engaged in ⟨function*ary*⟩ ⟨sedition*ary*⟩
²**-ary** \"\ *adj suffix* [ME *-arie*, fr. MF & L; MF *-aire*, fr. L *-arius*] : of or belonging to or connected with ⟨budget*ary*⟩ ⟨discretion*ary*⟩ ⟨parliament*ary*⟩ ⟨unit*ary*⟩
ar·ya *like next without* n\ *n, pl* **aryas** *also* **arya** *usu cap* [Skt *ārya*] : ARYAN
¹**ar·yan** *also* **ar·ian** \'a(a)rēən, 'er-, 'är- *sometimes* 'ärēən *or* 'äryən *or* 'arē- *or* 'āy-\ *adj, usu cap* [Skt *ārya*, adj. & n., noble, Aryan, member of the upper castes, prob. fr. *ari* stranger, enemy; akin to Av *airyō* Aryan, OPer *ariya*, and prob. to L *alius* other — more at ELSE] **1** : of or relating to the Indo-European family of languages or to their hypothetical proto-European language **2** : of or relating to speakers of Indo-European languages **3 a** : of or relating to a hypothetical ethnic type illustrated by or descended from early speakers of Indo-European languages **b** : NORDIC **4** : of or relating to the Indo-Iranians or their speech
²**aryan** *also* **arian** \"\ *n* -S *usu cap* [Skt *ārya*] **1** : a member of the Indo-European-speaking people one branch of which early occupied the Iranian plateau while another branch entered India and conquered and amalgamated with the earlier non-Indo-European inhabitants : INDO-IRANIAN **2 a** : member of the people that spoke the language from which the Indo-European languages are derived **b** : an individual of any of those peoples who have spoken these languages since prehistoric times : INDO-EUROPEAN **c** : NORDIC **d** : GENTILE **3** : a member of the Indo-European-speaking modern peoples of India as opposed to the Dravidian-speaking ones
ar·yan·ism \-,nizəm\ *n* -S *usu cap* **1** : the doctrine popularized by Nazism that the so-called Aryan peoples possess superior capacities for government, social organization, and civilization **2** : the belief in the doctrine of Aryanism and acceptance of its social and ethical implications often accompanied by suppression of the so-called non-Aryan peoples (as the Jews) — compare NORDICISM
ar·yan·ist \-,nəst\ *n* -S *usu cap* : one who makes a special study of the facts bearing on the Aryan race as a homogeneous group; *specif* : one who argues the existence of the Aryan race or credits the hypothetical Aryans with racially superior capacities or traits
ar·yan·i·za·tion \,=(=)=nə'zāshən, -,nī'z-\ *n* -S *usu cap* : the act or process of aryanizing
ar·yan·ize \'=(=)=,nīz\ *vt* -ED/-ING/-S *often cap* **1** : to make Aryan in speech characteristics or culture **2** : to clear of non-Aryan (as Semitic) personnel, control, or influence
ar·y·bal·los *or* **ar·y·bal·lus** \,arə'baləs\ *n* -ES [Gk *aryballos* bag, purse, aryballos, perh. fr. *ary-* (fr. *aryein* to draw — water) + *-ballos* (fr. *ballein* to throw) — more at DEVIL] : a flask or bottle that has a short neck, single handle, small orifice with a flaring lip, and globular body often elaborately decorated and that is used for holding oils or ointments — compare ALABASTRUM


aryballos

ar·y·epiglottic \¦arē + ¦==¦==\ *adj* [Gk *ary-* (fr. *aryein* to draw — water) + E *epiglottic*] : ARYTENOEPIGLOTTIC
ar·yl \'arəl\ *n* -S [ISV *aromatic* + *-yl*; prob. orig. formed in G] **1** : a univalent aromatic radical (as phenyl or tolyl) derived from an arene by removal of one hydrogen atom from a carbon atom of the nucleus — compare ARALKYL **2** : a compound of one or more aryl radicals with a metal ⟨sodium ~s⟩
ar·yl·amine \,arəl+\ *n* -S [ISV *aryl* + *amine*] : an amine (as aniline) containing aryl attached to amino nitrogen
ar·yl·a·mi·no \¦==¦mē(,)nō, -¦amə,nō\ *adj* [ISV *arylamino-*, fr. *arylamine*] : of, relating to, or containing an arylamine
ar·yl·ate \'arə,lāt\ *vt* -ED/-ING/-S [ISV *aryl* + *-ate*] : to introduce one or more aryl groups into (a compound)
ar·yl·a·tion \,==¦lāshən\ *n* -S : the act or process of arylating
ar·yl·ene \'arə,lēn\ *n* -S [ISV *aryl-* + *-ene*] : a bivalent radical (as phenylene) derived from an aromatic hydrocarbon by removal of a hydrogen atom from each of two carbon atoms of the nucleus
ar·yl·ide \-,līd\ *n* -S [*aryl* + *amide*] : a usu. acid amide (as an anilide) in which hydrogen of the amido group is replaced by aryl (as phenyl)
ar·yl·oxy \-¦läksē\ *adj* [*aryloxy-*, fr. *aryl* + *oxy-*] : of, relating to, or containing a univalent radical ArO (as phenoxy) composed of an aryl radical united with oxygen
¹**ar·yo-dravidian** \¦a(a)rē,ō, ¦er-, ¦är- *sometimes* 'ärē,ō *or* 'är(,)yō *or* 'arē,ō *or* 'ā(,)yō+\ *adj, usu cap A&D* [*Aryo-* (fr. ¹*Aryan*) + *Dravidian*] : of, relating to, or characteristic of the Indian people having a mixture of Aryan and Dravidian blood that constitute the chief population of northern India between the Punjab and Bengal and of the southern half of Ceylon
²**aryo-dravidian** \"\ *n* -S *cap A&D* : one of the Aryo-Dravidian people
aryo-indian \"+\ *n, cap A&I* : a person of a native race in India having an Aryan element in his ancestry
ar·y·te·no·epiglottic \¦arə¦tē(,)nō, ə¦rit^ən(,)ō+\ *or* **ar·y·te·no·epiglottidean** \"+\ *adj* [*aryteno-* (fr. NL *arytenoides*) + *epiglottic* or *epiglottidean*] : relating to or linking the arytenoid cartilage and the epiglottis ⟨~ folds⟩
¹**ar·y·te·noid** \,arə'tē,nȯid, ə'rit^ən,ȯid\ *also* **ar·y·te·noi·dal** \¦arə(,)tē¦nȯid^əl, ə¦rit^ən¦ȯi-\ *adj* [*arytaenoid* fr. NL *arytae-*

-*ite*] : a mineral consisting of a basic copper sulfate with copper chloride occurring as bluish green incrustations
¹**as** \əz, (')az\ *adv* [ME *as*, *alse*, *alswa*, adv. & conj., fr. OE *alswā*, *ealswā*, *ealswā* just as, likewise — more at ALSO] **1** : to the same degree or amount : to such an extent : EQUALLY — used to modify an adjective or an adverb ⟨I haven't found any new poems ~ good as my old favorites —Randall Jarrell⟩ ⟨neither of them wrote ~ well after the experience as before it —Van Wyck Brooks⟩ ⟨nowhere else in the world is there a people ~ intelligent or ~ perceptive of humor —F.P.Adams⟩ **2** : for instance : by way of example : THUS — usu. used to introduce illustrative details ⟨high-pitched sounds come to suggest spatial height, ~ in bird songs —Thomas Munro⟩
²**as** \"\ *conj* [ME *as*, *alse*, *alswa*] **1** : to which (degree or amount) : in which (degree or extent) : in or to the same degree in which — usu. used as a correlative after an adjective or adverb modified by adverbial *as* or *so* and often followed by a noun or pronoun representing an incomplete clause whose verb would be the same as that of the main clause ⟨the position of this science is as honorable ~ it is secure —L.A.White⟩ ⟨no general presentation . . . can interest the children as much ~ the learning of the foreign language —Ruth Mays⟩ ⟨his dull red hair was snow-powdered nearly as white ~ that of a British grenadier⟩ **2** : in the same way or manner that : in the form or condition in which ⟨his hair is brown ~ are his eyes⟩ ⟨studied the simile ~ Horner used it⟩ — sometimes followed by a noun or pronoun representing an incomplete clause whose verb would be the same as that of the main clause ⟨during his stay on the island he lived ~ an islander⟩ **3** : according to what : in accordance with that which or the way in which ⟨~ he said, the stream was full of trout⟩ ⟨his criticisms, ~ I remember, were coldly received⟩ ⟨he is really quite good ~ boys go⟩ **4** : as if ⟨were saying farewell to each other ~ to their childhood —Edith Sitwell⟩ ⟨this mechanical thought is crushing ~ with an iron roller all that is organic —W.B.Yeats⟩ **5** : during or at the same time that : WHILE, WHEN ⟨promptly opened fire again ~ he turned away —C.S.Forester⟩ ⟨~ he paced back and forth the idea occurred to him⟩ ⟨you will see the tower ~ you cross the bridge⟩ **6** : notwithstanding the degree to which : THOUGH ⟨some see in him, Gael ~ he was, the earliest Protestant —Gilbert Highet⟩ **7** : in a manner or degree befitting or having equal certainty with the fact, belief, or hope that ⟨this swears he, ~ he is a prince, is just and ~ I am a gentleman, I credit him —Shak.⟩ ⟨~ I live, I cannot believe it⟩ **8** : for the reason that : BECAUSE, SINCE ⟨remained in great loneliness and considerable privation ~ he had no income —W.L.Sullivan⟩ **9** *dial* : THAN — used in comparisons ⟨he better not be later ~ midnight —T.B.Costain⟩ **10 a** : that the result is : THAT — used with preceding *so* or *such* ⟨so clearly guilty ~ to leave no doubt of his conviction⟩ ⟨and such a son ~ all men hailed me happy —John Milton⟩ **b** : THAT — used to introduce a noun clause and now dial. except in certain negative expressions with *know*, *say*, or *see* that have wide usage in informal speech ⟨he said ~ he would come⟩ ⟨I don't know ~ it makes any difference⟩ **c** *dial* : in so far as : THAT — used to introduce an adverbial clause ⟨he hasn't come out again ~ I've seen⟩ — **as is** \(')a'ziz, ,ə'z-\ : in its present condition : without any repairs, improvements, or alterations being made ⟨the car was priced at $1000 *as is*⟩ — **as it were** : as if it were so : in a manner of speaking ⟨her triumph, *as it were*, did not last long⟩ — **as new** : practically new : in the best secondhand condition ⟨the clothes offered for sale were all prewar and all *as new*⟩ — **as you were** — a military command used (1) to cancel another command that has not yet been executed or (2) to direct troops to return to the position occupied before the last command
³**as** \"\ *pron* **1 a** : THAT, WHO, WHICH — used to introduce an adjectival clause and having *same* or *such* as antecedent ⟨their children should grow up in the same intellectual culture ~ they have enjoyed —G.B.Jeffery⟩ ⟨tears such ~ angels weep burst forth —John Milton⟩ **b** *now dial* : THAT, WHO, WHICH — used to introduce an adjectival clause and having a noun or pronoun as antecedent ⟨a lot of things happened . . . ~ never ought to —Richard Llewellyn⟩ ⟨was going to tell the gospel to them ~ had ears —R.P.Warren⟩ **2** : a fact that : THAT ⟨he is a foreigner, ~ is evident from his accent⟩ ⟨I have used thee, filth ~ thou art, with humane care —Shak.⟩
⁴**as** \"\ *prep* [¹*as*] **1** : after the manner of : the same as : LIKE ⟨had seen strong men become ~ weaklings when they were faced with . . . being shipwrecked —H.A.Chippendale⟩ ⟨his face was ~ a mask of gauze through which nothing was quite clearly visible —Max Beerbohm⟩ **2 a** : in the character, role, function, capacity, condition, or sense of ⟨more interested in . . . attitudes ~ attitudes than he is in their definition and embodiment in aesthetic forms —Mark Schorer⟩ ⟨eager for power ~ power⟩ ⟨his appearance ~ Hamlet⟩ ⟨his appointment ~ instructor⟩ **b** : in a way or of a nature constituting ⟨he comes home at six ~ a rule⟩ ⟨~ a result of the trip he was exhausted⟩ **c** : for consideration or considered in a specified form or relation — usu. used before prepositions and participles (as *against, between, distinguished*, and *opposed*) ⟨his argument ~ against yours⟩ ⟨my opinion ~ distinguished from theirs⟩
⁵**as** \'as\ *n, pl* **as·ses** \'a(,)sēz, -,səz\ [L — more at ACE] **1** : LIBRA 2 **2 a** (1) : a bronze coin of the ancient Roman republic varying in weight from 1 as, or 12 ounces, to ½ ounce (2) : one of several similar coins issued by some of the Roman emperors **b** : a unit of value equivalent to an as coin


Roman as, showing head of Janus

⁶**as** *sing of* AESIR
⁷**as** \'äs\ *also* **as nas** \-näs\ *n* [Per] : a Persian card game similar to poker and by some thought to be its progenitor
¹**as-** — see AD-
²**as-** *also* **asym-** *comb form, usu ital* [ISV *asymmetric*] : asymmetric — in names of organic compounds ⟨*as*-dichloro-ethylene⟩
-as *pl of* -A
AS *abbr* **1** account sales **2** after sight **3** air service **4** air speed **5** alongside **6** [ML *anno salutis*] in the year of redemption **7** antisubmarine **8** applied science **9** apprentice seaman **10** at sight
As *symbol* arsenic
a's *or* **as** *pl of* A
asa·do \ə'sä(,)dō\ *n* -S [AmerSp, fr. Sp, roast meat, fr. *asado* (past part. of *asar* to roast), fr. L *assatus*, past part. of *assare* to roast, fr. *assus* roasted; akin to L *ardere* to burn — more at ARDOR] : BARBECUE
asa dul·cis \¦asə'dəlsəs, ¦äs-\ *n* [NL, lit., sweet gum] : BENZOIN 1
as·a·fet·i·da *or* **as·a·foet·i·da** *or* **as·sa·fet·i·da** *or* **as·sa·foet·i·da** \,asə'fid·ədē, -fed·ə-, -fetə-, as'f-, aas-,ais-; -fed·ədə, -fetədə\ *also* **as·fet·i·da** \as'f-,aas'f-,ais'f-\ *n* -S [ME *asafetida*, fr. ML *asafoetida*, fr. *asa* gum (of Iranian origin; akin to Per *azā* mastic) + L *foetida*, fem. of *foetidus* fetid] : the fetid gum resin of various Persian and East Indian plants of the genus *Ferula* (esp. *F. assafoetida*, *F. foetida*, or *F. narthex*) occurring in the form of tears and dark-colored masses, having a strong odor and taste, and formerly used in medicine as an antispasmodic
asa·hi·ka·wa \¦äsəhē¦käwə\ *adj, usu cap* [fr. *Asahikawa*, city on Hokkaido island, Japan] : of or from Asahikawa, Japan : of the kind or style prevalent in Asahikawa

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TO
LANTHANIDES

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and is undergoing clinical investigation in the United States. Because of a different mechanism of action, biguanides might be used instead of or in combination with sulfonylureas.

Phenformin. Phenformin hydrochloride [*834-28-6*] (1-phenethylbiguanide, *N*-(2-phenylethyl)imidodicarbonimidic diamide), is a white to off-white odorless crystalline power having a bitter taste. The melting point is 175–178°C. It is freely soluble in water and alcohol, and practically insoluble in chloroform, ether, and hexane. Its pH in solution is 6.0–7.0.

Metformin. Metformin [*657-24-9*] (1,1-dimethylbiguanide), mol wt 129.17, forms crystals from propanol, mp 218–220°C, and is soluble in water and 95% ethanol, but practically insoluble in ether and chloroform. Metformin, an investigational drug in the United States, does not increase basal or meal-stimulated insulin secretion. It lowers blood glucose levels in hyperglycemic patients with Type II diabetes but has no effect on blood glucose levels in normal subjects. It does not cause hypoglycemia. Successful metformin therapy usually is associated with no or some weight loss.

Clinical studies have shown that metformin is as effective as chlorpropamide, tolbutamide, or gliclazide in lowering fasting and post-prandial hyperglycemia in patients with newly diagnosed Type II diabetes. However, metformin treatment produces a modest mean weight loss of 1–2 kg as compared with a mean weight gain of 1.5–5.0 kg produced by sulfonylurea therapy. Therapy using metformin results in better glycemic control in about 80% of both obese and nonobese patients having newly diagnosed Type II diabetes. Reported rates of primary failure with metformin are about 12%, and those of secondary failure are about 5%.

Inhibitors of α-Glucosidase. Acarbose [*56180-94-0*] (*O*-4,6-dideoxy-4-[[[1*S*-(1α,5β,6α)]-4,5,6-trihydroxy-3-(hydroxymethyl)-2-cyclohexen-1-yl]amino]-α-D-glucopyranosyl-(1→4)-*O*-α-D-glucopyranosyl-(1→4)-D-glucose), with mol wt 645.63, is an investigational drug. It is a pseudotetrasaccharide isolated from strains of *Actinoplanes* and contains an unsaturated cyclitol moiety.

Acarbose is a nonabsorbable α-glucosidase inhibitor which blocks the digestion of starch, sucrose, and maltose. The digestion of complex carbohydrates is delayed and occurs throughout the small intestine rather than in the upper part of the jejunum. Absorption of glucose and other monosaccharides is not affected. Acarbose is administered orally three times a day and chewed with the first mouthful of food.

Miscellaneous Agents

Diazoxide [*364-98-7*] (3-methyl-7-chloro-1,2,4-benzothiadiazine 1,1-dioxide) is a nondiuretic thiazide used for its hyperglycemic actions when given orally (Proglycem) and for its antihypertensive effects when given intravenously (Hyperstat I.V.) (see CARDIOVASCULAR AGENTS). Diazoxide produces a prompt dose-related increase in blood glucose by directly inhibiting insulin secretion and, possibly, by stimulating epinephrine secretion by the adrenal medulla (see EPINEPHRINE AND NOREPINEPHRINE). Diazoxide is used to counteract hyperinsulinism in conditions such as insulinoma. It is not indicated in the treatment of functional hypoglycemia.

Diabetes, Insulin Resistance, Hyperinsulinemia and Vascular Disease: A Therapeutic Challenge for the 90s

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Introduction

Diabetes mellitus is a complex metabolic disease in which the metabolism of carbohydrate, lipid and protein is significantly altered. The disease exists in two clinical forms: insulin dependent (IDDM) and non-insulin dependent (NIDDM) diabetes. IDDM accounts for 15-25% of the diabetic population of the United States, and is believed to be the result of autoimmune destruction of pancreatic islet β-cells [1]. These patients rely on the exogenous administration of insulin to sustain their lives. The vast majority of the estimated 15 million Americans with diabetes have the non-insulin dependent form. This heterogeneous disorder is characterized by impaired insulin secretion and insulin resistance [2-5]. In addition to diabetes, the insulin resistant state is also seen in non-diabetics who become overweight. Tissue sensitivity to insulin, in these individuals, decreases by about 35% when ideal body weight is exceeded by 35-40% [6-8]. In spite of a considerable impairment in the efficiency of insulin, glucose tolerance remains relatively constant in this group due to the ability of the pancreatic β-cells to hypersecrete insulin that offsets the resistance [9]. This compensation results in a marked hyperinsulinemia that can be observed in both diabetic and non-diabetic, insulin-resistant individuals. A body of evidence is accumulating in the literature relating hyperinsulinemia, insulin resistance and vascular disease. The purpose of this review is not to provide an extensive examination of those studies, but rather to highlight some of the salient data, and the therapeutic options available, as well as to point out opportunities for further drug discovery research.

Insulin Resistance, Hyperinsulinemia and Vascular Disease

Himsworth was the first to describe insulin resistance in 1936 when he made the observation that many elderly and obese diabetic patients were relatively insensitive to the hypoglycemic action of insulin [10]. While the term insulin resistance is most commonly used to describe insulin's action on glucose homeostasis, this hormone has pleiotropic effects. Insulin resistance can, therefore, be described in terms of the biochemical and physiological changes that result from an impaired action of this hormone. Included in these effects are dyslipidemia characterized by hypertriglyceridemia [11-13], decreased high density lipoproteins (HDL) [14], and to a lesser extent, raised total and low density lipoprotein (LDL) cholesterol [14], hypertension [15-18], and a thrombotic diathesis associated with attenuated fibrinolysis [19,20]. Indeed, the clustering of insulin resistance, hypertriglyceridemia, and low plasma HDL cholesterol in the same individuals led Reaven to refer to them collectively as 'Syndrome X' [21].

Given the above findings, it is not surprising that individuals with NIDDM have a high incidence of premature atherosclerosis and increased morbidity and mortality from coronary artery disease, cerebrovascular disease and peripheral vascular disease [22,23]. It has been estimated that, despite the improvement over the years in diabetic patient care, the age-adjusted incidence of acute coronary events is six times greater in male diabetics and four times greater in female diabetics than in non-diabetics, independent of LDL cholesterol, HDL cholesterol, blood pressure and smoking [23].

Epidemiology of Insulin Resistance and Vascular Disease

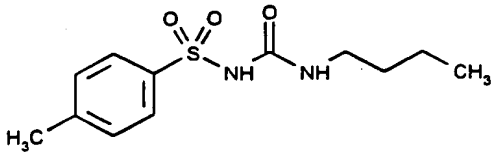
Several investigators have attempted to determine whether or not an association exists between the development of atherosclerosis and insulin resistance/hyperinsulinemia that is independent of the known risk factors of dyslipidemia, hypertension, hyperglycemia and obesity. Epidemiological studies have consisted of cross-sectional and prospective studies in both the general population and in diabetics [24]. While numerous studies have been carried out, a few should be discussed in particular because of the large numbers of patients included, the design of the studies, and the impact they have had on our current perceptions.

In 1985, Pyörälä and co-workers [25] published the results of a nine and a half year prospective study based on a cohort of 982 Helsinki policemen who were free of coronary disease at entry and were followed for the appearance of 'hard cardiac endpoints'. Multivariate analysis of the data showed that high plasma insulin 1 hr and 2 hr following an oral glucose load were found to be significant risk factors for the development of coronary heart disease (CHD) that was independent of other risk factors.

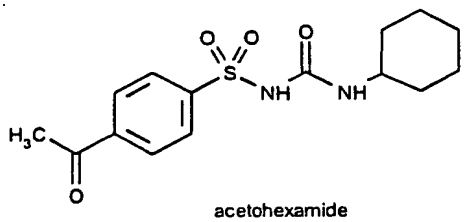
The Paris Prospective study examined fatal and non-fatal CHD in over 7000 male civil service workers, and reported results at 5 [26], 10 [27], and 15 years [28]. At the 15 year follow up, 2 hr post-load insulin remained a significant, independent predictor of death from CHD.

Recently, Solymoss and coworkers [29] studied 1119 French Canadians undergoing elective coronary arteriography for the evaluation of potential coronary artery disease. They examined the correlations between fasting serum insulin levels, the general features of insulin resistance, and various aspects of CHD. Patients were classified according to the quartiles of serum insulin. Those patients in the top quartile had an increased body mass index, serum triglycerides and decreased HDL cholesterol. Significantly more women in the fourth quartile had angiographically demonstrable significant stenosis of the coronary arteries, and previous myocardial infarction than those in the first quartile. There was a tendency for a

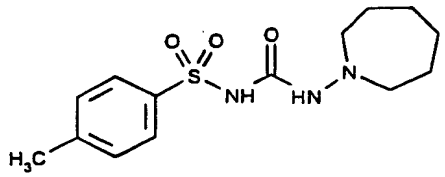
Figure 1. Sulfonylureas



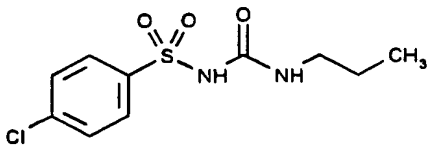
tolbutamide



acetohexamide



tolazamide



chlorpropamide

greater incidence of previous myocardial infarction in men in the fourth quartile relative to the first quartile, but this did not reach statistical significance.

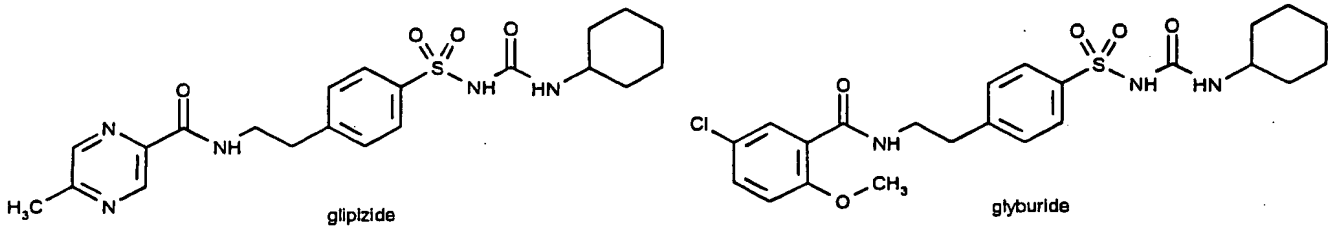
A number of cross-sectional studies have indicated that insulin treatment of NIDDM, and hence hyperinsulinemia, is strongly associated with CHD mortality [30, 31, 32], while a number of prospective studies have failed to find differences in cardiovascular disease morbidity and mortality as a function of insulin treatment. These include the University Group Diabetes Program (UGDP) [33] and the Diabetes Control and Complications Trial (DCCT) [34]. An excellent review of both of these seminal studies has been published [35]. The UGDP study compared diet therapy for NIDDM with standard insulin therapy and variable-dose insulin regimen, as well as administration of oral agents, on the incidence of cardiovascular and microvascular outcomes. The DCCT study, which examined the effects of conventional versus intensive management of IDDM on microvascular and neurological complications, was not primarily designed to test the effects of glucose control on the risk for macrovascular disease. The results of the UGDP study failed to show significant differences in cardiac or macrovascular endpoints when comparing the diet therapy group to the standard insulin or variable insulin therapy groups. After considerable sub-grouping and analysis of the data, the study committee concluded that, using a strict intention-to-treat criteria, no evidence exists that insulin therapy is superior to (or worse than) diet therapy alone for reducing the risk of vascular disease. The DCCT study on the other hand, showed far fewer cardiovascular events in the intensively treated group and a trend toward a reduction in the risk for cardiac and peripheral vascular events that failed to reach statistical significance [34].

The evidence that these large, long-term, randomized studies provide does not resolve the issues relating to hyperinsulinemia, insulin resistance and vascular disease. Genuth [35] has provided some insight as to why definitive answers were not obtained. However, both of these studies were designed to test the glucose toxicity hypothesis. That is, hyperglycemia, or poor glucose control, leads to the development of vascular disease. The proof for this hypothesis was not definitively obtained in the UGDP study, and the DCCT study was focused on microvascular events. However, it is also quite possible that glycemic control is only part of the pathologenetic process and that insulin resistance *per se* is a major contributor. None of the above mentioned studies made measurements of insulin sensitivity, and with good reason. Estimation of insulin sensitivity by the hyperinsulinemic, euglycemic clamp [36] is laborious and not suited to high throughput studies. In essence, the technique measures the rate of glucose disposal in individuals given a fixed, supraphysiologic level of insulin. As a physiologic equivalent, it might be quite useful to describe glycemic control in terms of the glucose-insulin ratio. This parameter would give an assessment of how much insulin is required to maintain the measured plasma glucose. Such a measurement would allow somewhat of an equalization of estimates of insulin sensitivity across a range of levels of glycemia. Additionally, it would provide an estimate of the level of insulin resistance to population based studies attempting to determine the role of that factor in the complications of diabetes.

Pre-clinical Studies

In addition to the population studies implicating hyperinsulinemia in cardiovascular disease, a number of experimental findings have given some insight as to potential mechanisms for the role of this hormone in vascular disease. Insulin receptors have been identified in rat [37], bovine [38,39], and human [40] smooth muscle cells. It has also been shown to be mitogenic for these cells [41-44]. Insulin can stimulate lipid metabolism in smooth muscle cells from the rat [45] and can increase the binding of LDL to bovine smooth muscle cells [39] and human monocytes [46]. The activity of the rate limiting enzyme of cholesterol biosynthesis, 3-hydroxy,3-methylglutaryl coenzyme A reductase, is also increased in human monocytes by insulin treatment [47]. Several studies have attempted to examine the role of insulin in atherogenesis *in vivo*; these have been reviewed by Stout [48]. Most of the effects observed in these experiments have been

Figure 2. Second generation sulfonylureas



modest at best, with respect to the development of atherosclerosis. The literature is replete with references to the work of Duff [49,50] and McGill [51] regarding their observations concerning the role of insulin in the development of atherosclerosis in cholesterol-fed diabetic rabbits.

These investigators found that alloxan-induced diabetes would increase plasma cholesterol levels in rabbits, but decreased the arterial lesions in cholesterol fed rabbits relative to control, cholesterol-fed rabbits. Alloxan treated animals that failed to develop diabetes had the same degree of vascular lesions as control animals. When animals were treated with insulin, the degree of cholesterol deposition in the aorta of the diabetic rabbits was very similar to that of the controls [50]. However, recent work by Zilversmit and co-workers has demonstrated that the reason for this observation is probably related to impaired lipolysis of triglyceride-rich lipoproteins in untreated diabetic animals. This results in the formation of very large lipoproteins that are unable to enter the artery wall [52-55] and hence, cannot participate in the atherogenic process.

Current and Emerging Therapies

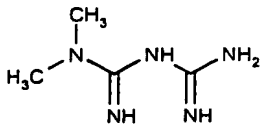
The studies reported in the literature have not unequivocally implicated insulin resistance or hyperinsulinemia in vascular disease, nor have they exonerated it as a causal factor. In order to answer such questions, and to effectively treat NIDDM, it is necessary to have pharmacological agents that are capable of ameliorating insulin resistance without creating hyperinsulinemia. Several treatment options are available for controlling the metabolic abnormalities of NIDDM. Since obesity alone has been shown to cause insulin resistance and obesity is a major problem in NIDDM, a program of diet, weight loss and exercise can result in an improvement in insulin sensitivity without increasing plasma insulin levels [9]. Treatment with insulin in many cases will improve tissue sensitivity to the hormone. This enhanced sensitivity has been shown to improve markedly even when normoglycemia has been achieved by administering doses of over 100 units per day [56].

In lieu of insulin for the treatment of NIDDM, several orally active agents are available, including the sulfonylureas and metformin [57]. The sulfonylureas, (Figure 1), exemplified by tolbutamide, acetohexamide, tolazamide, and chlorpropamide, have been available for a considerable period of time. These agents stimulate the secretion of insulin in the absence of other secretagogues [58]. *In vivo*, their main effect is to sensitize the β-cell to glucose. They do not increase the synthesis of insulin. While the various sulfonylureas differ in pharmacokinetic properties, there is no evidence that their mechanisms of action are different [59,73]. The so-called second generation sulfonylureas glipizide and glyburide (Figure 2) are the most potent agents in this class. They have been estimated to be 100 to 150 times more potent than tolbutamide on a molar basis [59,73]. The sulfonylureas are reasonably well tolerated. However, it has been estimated [57] that after 10 years, only about 50% of the patients initially started on this class of agents continue to have satisfactory control. Metformin, an agent recently approved for use in the United States and used for many years in Europe, is a member of the biguanide class of compounds (Figure 3). Other agents in this class include buformin and phenformin. Phenformin was used in the US for many years, but was withdrawn because of a high incidence of lactic acidosis [60]. Metformin has been used for a number of years in Europe. It appears to act by increasing peripheral and hepatic sensitivity to insulin without altering insulin secretion [61]. In comparison with sulfonylureas, this agent rarely causes hypoglycemia. Metformin's most common side effects are gastrointestinal. Lactic acidosis is rare, but can be fatal [57].

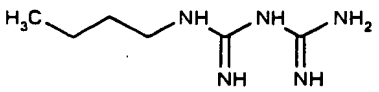
A relatively new class of agents, the thiazolidinedione derivatives (Figure 4), that improve peripheral insulin sensitivity are currently under development. Representative agents include ciglitazone, pioglitazone, englitazone, and troglitazone. These analogs have been shown to be effective in reducing hypoglycemia in various animal models including Zucker rats, ob/ob mice, and KKA^y mice [62,63]. The hypoglycemic effects observed in the various animal models are associated with improvements in insulin sensitivity and without effect on insulin secretion. These agents do not produce hypoglycemia in the euglycemic state. Troglitazone, a compound in this class, is most interesting in that it contains the pentamethylhydroxychroman of vitamin E coupled to the thiazolidinedione. This gives the compound a certain amount of antioxidant activity that may be important in protecting LDL from oxidation [64]. Treatment with this agent completely prevented the development of insulin resistance, hypertension and hypertriglyceridemia in fructose-fed rats [65]. Troglitazone is not insulinomimetic *per se*, but does improve insulin sensitivity in streptozotocin-diabetic rats [66], as well as in normal animals [67].

Data concerning troglitazone are beginning to emerge from clinical trials. When 11 obese patients with NIDDM were treated with the drug for a period of 6 -12 weeks, eight showed significant improvement in overall glycemic control, improvement in insulin sensitivity, and a reduction in plasma insulin levels [68]. In a double-blind, placebo-controlled study, treatment of diabetic patients with troglitazone over a three month period resulted in

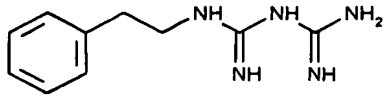
Figure 3. Biguanides



metformin

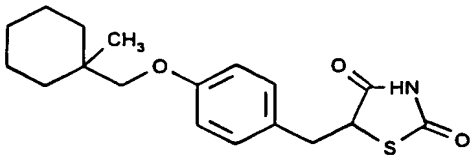


buformin

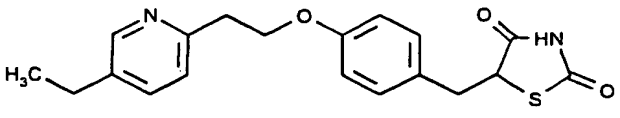


phenformin

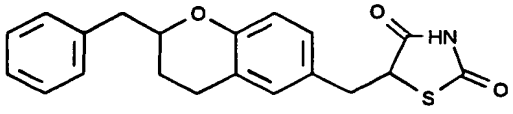
Figure 4. Thiazolidinedione derivatives



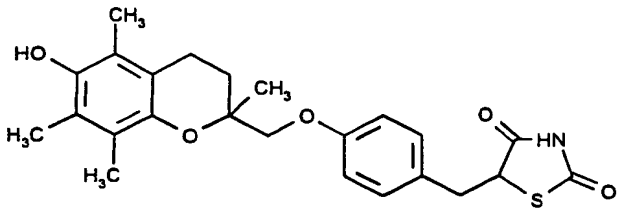
ciglitazone



pioglitazone



englitazone



troglitazone

significant improvement in hyperglycemia, insulin resistance and plasma free fatty acid levels [69]. Iwamoto.and coworkers [70] studied 19 NIDDM patients whose glycemic control was considered stable but unsatisfactory with diet and/or sulfonylurea therapy. Treatment with troglitazone resulted in significant improvement in glycemic control and insulin sensitivity without altering insulin secretion. The actions of this compound may also be important in preventing the onset of diabetes in obese individuals with impaired glucose tolerance. Eighteen non-diabetic, obese individuals were treated with either troglitazone or placebo for 12 weeks. Drug treatment resulted in improvement in glucose tolerance and a decrease in insulin resistance [71]. Ogihara and colleagues used troglitazone to treat 18 individuals with essential hypertension complicated by mild NIDDM [72]. An eight week course of therapy resulted in decreases in fasting plasma·glucose, fasting plasma insulin and a significant reduction in blood pressure. The reduction in blood pressure correlated significantly with the decrease in plasma insulin. These studies demonstrate that pharmacological intervention with troglitazone in NIDDM and in impaired glucose tolerance in obese individuals results in improvement in biochemical and physiological aberrations associated with insulin resistance and hyperinsulinemia, while simultaneously improving total body sensitivity to this hormone.

Conclusions

The concept that insulin resistance and/or hyperinsulinemia are contributory factors for the development of vascular disease has been debated in the literature for almost 30 years. While the data are far from conclusive, a large body of laboratory and animal studies have

demonstrated a certain plausibility to the notion. The clinical and population based studies have been complicated by the confounding effects between hyperinsulinemia, obesity, dyslipidemia, hypertension and other classic risk factors. Also missing is some uniform, ready estimate of the degree of insulin resistance in any given individual or group of individuals. Calculation of the fasting or post-prandial glucose-insulin ratio may provide such a measure and help to clarify future studies.

Most treatment options provide for glycemic control by inducing the secretion of insulin, or by providing pharmacologic doses of exogenous insulin. The biguanide metformin, and the advent of the thiazolidinedione class of 'insulin enhancing' agents promise to provide for glycemic control without stimulating insulin secretion, thereby reducing total exposure to this very potent hormone. The latter class of agents appear to be well tolerated, devoid of hypoglycemic liability, and have shown clinical promise under a number of experimental paradigms. The availability of such agents may provide very useful tools for the study of the involvement of insulin resistance and hyperinsulinemia in vascular disease.

References

1. Eisenbarth GS. **Type I diabetes mellitus: a chronic autoimmune disease.** *N Eng J Med* (1986) **314:** 1360-1368.
2. Lillioja S, Mott DM, Howard BV. **Impaired glucose tolerance as a disorder of insulin action: longitudinal and cross-sectional studies in Pima Indians.** *N Engl J Med* (1988) **318:** 1217-1225.
3. DeFronzo RA, Ferrannini E, Kolvisto V. **New concepts in the pathogenesis of non-insulin-dependent diabetes mellitus.** *Am J Med* (1983) **74:** 52-81.
4. Turner RC, Matthews DR, Clark A, O'Rahilly S, Rudenski AS, Levy J. **Pathogenesis of NIDDM - a disease of deficient insulin secretion.** *Baillieres Clin Endocrinol Metab* (1988) **2:** 327-342.
5. Gerich JE. **Role of insulin resistance in the pathogenesis of type 2 (non-insulin dependent) diabetes mellitus.** *Baillieres Clin Endocrinol Metab* (1988) **2:** 307-326.
6. DeFronzo RA, Sherwin RS, Nendler R, Felig P. **Insulin binding to monocytyes and insulin action in human obesity, starvation and refeeding.** *J Clin Invest* (1978) **62:** 204-213.
7. Bogardus C, Lillioja S, Mott D, Reaven GR, Kashiwagi A, Foley J. **Relationship between obesity and maximal insulin-stimulated glucose uptake *in vivo* and *in vitro* in Pima Indians.** *J Clin Invest* (1984) **73:** 800-805.
8. Bonnadonna R, Groop L, Kraemer N, DeFronzo RA. **Obesity and insulin resistance in man: a dose response study.** *Metabolism* (1990) **39:** 452-459.
9. DeFronzo RA. **Lilly Lecture 1987: The triumvirate: beta cell, muscle, liver: a collusion responsible for NIDDM.** *Diabetes* (1988) **37:** 667-687.
10. Himsworth HP. **Diabetes mellitus: its differentiation into insulin-sensitive and insulin-insensitive types.** *Lancet* (1936) **I:** 127-130.
11. Steiner G. **Hyperinsulinaemia and hypertriglyceridaemia.** *J Intern Med Suppl* (1994) **736:** 23-6.
12. DeFronzo RA, Ferrannini E. Insulin resistance. **A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease.** *Diabetes Care* (1991) **14:** 173-94
13. Reaven GM. **Insulin Resistance, Hyperinsulinemia, Hypertriglyceridemia, and Hypertension. Parallels Between Human Disease and Rodent Models.** *Diabetes Care* (1991) **14:** 195-202.
14. Flack JM, Sowers JR. **Epidemiologic and clinical aspects of insulin resistance and hyperinsulinemia.** *Am J Med* (1991) **91:** 118-215.
15. Sowers JR, Khoury S, Standley P, Zemel P, Zemel M. **Mechanisms of hypertension in diabetes.** *Am J Hypertens* (1991) **4:** 177-182.
16. Berne C. **Insulin resistance in hypertension - A relationship with consequences.** *J Intern Med* (1991) **735** (Suppl.): 65-73.
17. Rocchini AP. **Insulin resistance and blood pressure regulation in obese and nonobese subjects: Special lecture.** *Hypertension* (1991) **17:** 837-842.
18. Bonner G. **Hyperinsulinemia, insulin resistance, and hypertension.** J *Cardiovasc Pharmacol* (1994) **24:** S39-S49
19. Schneider DJ, Sobel BE. **Effect of diabetes on the coagulation and fibrinolytic systems and its implications for atherogenesis.** *Coron Artery Dis* (1992) **3:** 26-32.
20. Schneider DJ, Nordt TK, Sobel BE. **Attenuated fibrinolysis and accelerated atherogenesis in type II diabetic patients.** *Diabetes* (1993) **42:** 1-7.
21. Reaven GM. **Role of insulin resistance in human disease.** *Diabetes* (1988) **37:** 1495-1507.
22. Pan WH, Cedres LB, Liu K, *et al.* **Relationship of clinical diabetes and asymptomatic hyperglycemia to risk of coronary heart disease mortality in men and women.** *Am J Epidemiol* (1986) **123:** 504-516.
23. Uusitupa MI, Niskanen LK, Siltonen O, Voutilainen E, Pyorala K. **5-Year incidence of atherosclerotic vascular disease in relation to general risk factors, insulin level, and abnormalities in lipoprotein composition in non-insulin-dependent diabetic and non-diabetic subjects.** *Circulation* (1990) **82:** 27-36.
24. Elliott TG, Viberti G. **Relationship between insulin resistance and coronary heart disease in diabetes mellitus and the general population: a critical appraisal.** *Baillieres Clin Endocrinol Metab* (1993) **7:** 1079-1103.
25. Pyörälä K, Savolainen E, Kaukola S, Haapakoski J. **Plasma insulin as coronary heart disease risk factor: relationship to other risk factors and predictive value during 9 1/2 year follow-up of the Helsinki Policemen Study Population.** *Acta Med Scand* (1985) **701:** 38-52.
26. Ducimetiere P, Eschwege E, Papoz L. **Relationship of plasma insulin levels to the incidence of myocardial infarction and coronary heart disease mortality in a middle-aged population.** *Diabetologia* (1990) **19:** 205-210.
27. Eschwege E, Richard JL, Thibult N. **Coronary heart disease mortality in relation with diabetes, blood glucose, and plasma insulin levels: the Paris Prospective Study, ten years later.** *Horm Metab Res* (1985) **15:** 41-46.

28. Fontbonne A, Charles MA, Thibult N. **Hyperinsulinaemia as a predictor of coronary heart disease mortality in a healthy population: the Paris Propsective Study, 15 year follow up.** *Diabetologia* (1991) **34:** 356-361.

29. Solymoss BC, Marcil M, Chaour M, Gilfix BM, Poitras AM, Campeau L. **Fasting hyperinsulinism, insulin resistance syndrome, and coronary artery disease in men and women.** *Am J Cardiol* (1995) **76:** 1152-1156.

30. Kleinman JC, Donahue RP, Harris MI, Finucane FF, Madans JH, Brock DB. **Mortality among diabetics in a national sample.** *Am J Epidemiol* (1988) **128:** 389-401.

31. Garcia MJ, McNamara PM, Gordon T, Kannell WB. **Morbidity and mortality in diabetics in the Framingham population: 16 yr follow up study.** *Diabetes* (1974) **23:** 105-111.

32. Czyzk A, Krolewski AS, Szablowska S, Alot A, Kopczynski J. **Clinical course of myocardial infarction among diabetic patients.** *Diabetes Care* (1980) **3:** 526-529.

33. University Group Diabetes Program. **Effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. VIII. Evaluation of insulin therapy: final report.** *Diabetes* (1982) **31:** 1-78.

34. The Diabetes Control and Complications Trial Research Group. **The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus.** *N Engl J Med* (1993) **329:** 977-986.

35. Genuth S. **Exogenous insulin administration and cardiovascular risk in non-insulin-dependent and insulin-dependent diabetes mellitus.** *Ann Intern Med* (1996) **124:** 104-109.

36. DeFronzo RA, Tobin JD, Andres R. **Glucose clamp technique: a method for quantifying insulin secretion and resistance.** *Am J Physiol Endocrinol Metabol* (1979) **6:** E214-E223.

37. Pleifle B, Ditschuneit H. **Two separate receptors for insulin and insulin-like growth factor on arterial smooth muscle cells.** *Exp Clin Endocrinol* (1983) **81:** 280-286.

38. King GL, Kahn CR, Rechler MM, Nissley SP. **Direct demonstration of separate receptors for growth and metabolic activities of insulin and multiplication-stimulating activity (an insulin-like growth factor) using antibodies to the insulin receptor.** *J Clin Invest* (1980) **66:** 130-140.

39. Young IR, Stout RW. **Effects of insulin and glucose on the cells of the arterial wall: interaction of insulin with dibutyryl cyclic AMP and low density lipoprotein in arterial cells.** *Diabetes Metab* (1987) **13:** 301-306.

40. Pfeifle B, Ditschuneit HH, Ditschuneit H. **Binding and biological actions of insulin-like growth factors on human arterial smooth muscle cells.** *Horm Metab Res* (1982) **14:** 409-414.

41. Pfeifle B, Ditschuneit H. **Effect of insulin on growth of cultured human arterial smooth muscle cells.** *Diabetologia* (1981) **20:** 155-158.

42. Pfeifle B, Ditschuneit HH, Ditschuneit H. **Insulin as a growth regulator of rat arterial smooth muscle cells *in vitro*.** *Horm Metab Res* (1980) **12:** 381-385.

43. Weinstein R, Stemerman.M.B., Maciag T. **Hormonal requirements for growth of arterial smooth muscle cells *in vitro*: an endocrine approach to atherosclerosis.** *Science* (1981) **212:** 818-820.

44. King GL, Buzney SM, Kahn CR, *et al.* **Differential responsiveness to insulin of endothelial and support cells from micro- and macrovessels.** *J Clin Invest* (1983) **71:** 974-979.

45. Stout RW. **The effect of insulin and glucose on sterol synthesis in cultured rat arterial smooth muscle cells.** *Arteriosclerosis* (1977) **27:** 271-278.

46. Krone W, Naegele H, Behnki B, Greten H. **Opposite effects of insulin and catecholamines on LDL-receptor activity in human mononuclear leukocytes.** *Diabetes* (1988) **37:** 1386-1391.

47. Krone W, Greten H. **Evidence for post-transcriptional regulation by insulin of 3-hydroxy-3-methylglutaryl coenzyme A reductase and sterol synthesis in human mononuclear leukocytes.** *Diabetologia* (1984) **26:** 366-369.

48. Stout RW. **Insulin as a mitogenic factor: role in the pathogenesis of cardiovascular disease.** *Am J Med* (1991) **90:** 62S-65S.

49. Duff GL, McMillan GC. **The effect of alloxan diabetes on experimental cholesterol atherosclerosis in the rabbit. I. The inhibition of experimental atherosclerosis in alloxan diabetes. II. The effect of alloxan diabetes on the retrogression of experimental atherosclerosis.** *J Exp Med* (1949) **86:** 611-629.

50. Duff GL, Brechin DJH, Findelstein WE. **The effect of alloxan diabetes on experimental cholesterol atherosclerosis in the rabbit. IV. The effect of insulin therapy on the inhibition of atherosclerosis in the alloxan-diabetic rabbit.** *J Exp Med* (1954) **100:** 371-380.

51. McGill HC, Jr., Holman RL. **The influence of alloxan diabetes on cholesterol atheromatosis in the rabbit.** *Proc Soc Exp Biol Med* (1949) **72:** 72-73.

52. Minnich A, Zilversmit DB. **Impaired triacylglycerol catabolism in hypertriglyceridemia of the diabetic, cholesterol-fed rabbit: a possible mechanism for protection from atherosclerosis.** *Biochim Biophys Acta* (1989) **1002:** 324-332.

53. Nordestgaard BG, Zilversmit DB. **Comparison of arterial intimal clearances of LDL from diabetic and nondiabetic cholesterol-fed rabbits. Differences in intimal clearance explained by size differences.** *Arteriosclerosis* (1989) **9:** 176-183.

54. Nordestgaard BG, Zilversmit DB. **Hyperglycemia in normotriglyceridemic, hypercholesterolemic insulin-treated diabetic rabbits does not accelerate atherogenesis.** *Atherosclerosis* (1988) **72:** 37-47.

55. Nordestgaard BG, Zilversmit DB. **Large lipoproteins are excluded from the arterial wall in diabetic cholesterol-fed rabbits.** *J Lipid Res* (1988) **29:** 1491-1500.

56. Garvey WT, Olefsky JM, Griffin J, Hamman RF, Kolterman OG. **The effect of insulin treatment on insulin secretion and insulin action in type II diabetes mellitus.** *Diabetes* (1985) **34:** 222-234.

57. Gerich JE. **Oral hypoglycemic agents.** *N Engl J Med* (1989) 321: 1231-1245.

58. Grodsky GM, Epstein GH, Fanska R, Karam JH. **Pancreatic action of the sulfonyl-ureas.** *Fed Proc* (1977) **36:** 2714-2719.

59. Jackson JE, Bressler R. **Clinical pharmacology of sulfonylurea hypoglycemic agents: Part 2.** *Drugs* (1981) **22:** 211-245.

60. Williams RH, Palmer JP. **Farewell to phenformin for treating diabetes mellitus.** *Ann Intern Med* (1975) **83:** 567-568.

61. Dunn CJ, Peters DH. **Metformin. A review of its pharmacological properties and therapeutic use in non-insulin-dependent diabetes mellitus.** *Drugs* (1995) **49:** 721-749.

62. Fujiwara T, Okuno A, Yoshioka S, Horikoshi H. **Suppression of hepatic gluconeogenesis in long-term Troglitazone treated diabetic KK and C57BL/KsJ-db/db mice.** *Metabolism* (1995) **44:** 486-90.

63. Petrie JR, Donnelly R. **New pharmacological approaches to insulin and lipid metabolism.** *Drugs* (1994) **47:** 701-710.

64. Nagasaka Y, Kaku K, Nakamura K, Kaneko T. **The new oral hypoglycemic agent, CS-045, inhibits the lipid peroxidation of human plasma low density lipoprotein *in vitro.*** *Biochem Pharmacol* (1995) **50:** 1109-1111.

65. Lee MK, Miles PD, Khoursheed M, Gao KM, Moossa AR, Olefsky JM. **Metabolic effects of troglitazone on fructose-induced insulin resistance in the rat.** *Diabetes* (1994) **43:** 1435-9.

66. Tominaga M, Igarashi M, Daimon M, *et al.* **Thiazolidinediones (AD-4833 and CS-045) improve hepatic insulin resistance in streptozotocin-induced diabetic rats.** *Endocr J* (1993) **40:** 343-348.

67. Lee MK, Olefsky JM. **Acute effects of troglitazone on *in vivo* insulin action in normal rats.** *Metabolism* (1995) **44:** 1166-9.

68. Suter SL, Nolan JJ, Wallace P, Gumbiner B, Olefsky JM. **Metabolic effects of new oral hypoglycemic agent CS-045 in NIDDM subjects.** *Diabetes Care* (1992) **15:** 193-203.

69. Mimura K, Umeda F, Hiramatsu S, *et al.* **Effects of a new oral hypoglycaemic agent (CS-045) on metabolic abnormalities and insulin resistance in type 2 diabetes.** *Diabet Med* (1994) **11:** 685-91.

70. Iwamoto Y, Kuzuya T, Matsuda A, *et al.* **Effect of new oral antidiabetic agent CS-045 on glucose tolerance and insulin secretion in patients with NIDDM.** *Diabetes Care* (1991) **14:** 1083-6.

71. Nolan JJ, Ludvik B, Beerdsen P, Joyce M, Olefsky J. **Improvement in glucose tolerance and insulin resistance in obese subjects treated with troglitazone.** *N Engl J Med* (1994) **331:** 1188-93.

72. Ogihara T, Rakugi H, Ikegami H, Mikami H, Masuo K. **Enhancement of insulin sensitivity by troglitazone lowers blood pressure in diabetic hypertensives.** *Am J Hypertens* (1995) **8:** 316-20.

73. Jackson JE, Bressler R. **Clinical pharmacology of sulfonylurea hypoglycemic agents: Part 2.** *Drugs* (1981) **22:** 295-320.

1: Endocr Pract 2001 Jul-Aug;7(4):279-86

Use of insulin-sensitizing agents in patients with polycystic ovary syndrome.

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OBJECTIVE: To review the subject of polycystic ovary syndrome and the therapeutic use of insulin-sensitizing agents in patients with this endocrinopathy. METHODS: We present background information on thi disorder and summarize the pertinent published literature. RESULTS: Polycystic ovary syndrome affects approximately 7.5% of reproductive-age women in the United States. Although specific diagnostic criteria for this condition have not been established, the presence of three major factors-chronic anovulation, hyperandrogenemia, and clinical signs of hyperandrogenism-has been proposed as essential for consideration of the diagnosis. A high ratio of serum luteinizing hormone to follicle-stimulating hormone is found in 60 to 75% of wome with this syndrome. Treatment with metformin may yield heterogeneous responses in differing populations with polycystic ovary syndrome, but most studies have shown evidence of restoration of ovulatory cycling. In addition, weight loss and decreases in free and total testosterone levels have been reported. Troglitazone therapy proved somewhat less efficacious than metformin for restoring menstrual cycles and similar to metformin in producing hormonal responses. Because troglitazone is no longer available for clinical use, studies will need to be extended to other thiazolidinediones. Patients treated with another insulin sensitizer, D-chiro-inositol, have demonstrated improved insulin sensitivity, ovulatory rates, and biochemical findings. CONCLUSION: Current evidence suggests that the use of insulin-sensitizing agents in patients with polycystic ovary syndrome not only improves their sensitivity to the effects of insulin on glucose and lipid metabolism but also ameliorates clinical and biochemical manifestations of hyperandrogenism and increases rates of ovulation. Multicenter studies with larger numbers of patients are needed.

Publication Types:
- Review
- Review, Tutorial

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1: Arterioscler Thromb Vasc Biol 2001 Dec;21(12):1891-5

PPARgamma and atherosclerosis: effects on cell growth and movement.

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Atherosclerosis is a major vascular complication of diabetes and the primary cause of mortality in persons with this disease. Metabolic abnormalities related to the Insulin Resistance Syndrome or Metabolic Syndrome may importantly contribute to the increased risk of atherosclerosis associated with diabetes. Thiazolidinediones (TZDs) are oral insulin sensitizers in broad clinical use that enhance insulin-stimulated glucose uptake into skeletal muscle. TZDs can also improve cardiovascular risk factors and exert direct effects on vascular cells to potentially retard the atherosclerotic process. Direct vascular effects of TZDs likely result from their activity as ligands for the nuclear receptor, PPARgamma. All of the major cell types in the vasculature express PPARgamma, including intimal macrophages and vascular smooth muscle cells (VSMCs) in human atheroma. TZDs block VSMC growth by inducing cell cycle arrest in G1 through an inhibition of retinoblastoma protein phosphorylation. Migration of monocytes and VSMCs is also inhibited by TZDs, possibly through decreased matrix metalloproteinase production. Activation of PPARgamma by TZDs in macrophages induces ABCA1 transporter expression to promote reverse cholesterol transport. These antiatherogenic activities may also occur in vivo because TZDs have been shown to inhibit lesion formation in several animal models. Thus, TZD activation of PPARgamma may protect against atherosclerosis both by normalizing proatherogenic metabolic abnormalities of the insulin resistance/diabetes milieu and through an inhibition of vascular cell growth and movement.

Publication Types:
- Review
- Review, Tutorial

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1: Arch Dermatol 2000 May;136(5):609-16

Troglitazone improves psoriasis and normalizes models of proliferative skin disease: ligands for peroxisome proliferator-activated receptor-gamma inhibit keratinocyte proliferation.

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BACKGROUND: Psoriasis is often treated with agents that activate nuclear hormone receptors for glucocorticoids, retinoids, and vitamin D. The peroxisome proliferator-activated receptor-gamma (PPARgamma) is related nuclear hormone receptor that can be activated by its ligands, including the thiazolidinediones. OBJECTIVE: To assess whether treatment with troglitazone, a currently available thiazolidinedione used t treat diabetes mellitus, has an effect on psoriasis in normoglycemic patients and whether ligands for PPARgamma have an effect on models of psoriasis. DESIGN: Open-label administration of troglitazone in patients with psoriasis and evaluation of drug actions in cellular, organ, and transplant models of psoriasis. SETTING: University and community hospital outpatient departments and university laboratories. PATIENTS: Patients with chronic, stable plaque psoriasis and control subjects. Five patients with psoriasis received troglitazone (none withdrew); 10 different untreated patients and 10 controls provided tissue samples. INTERVENTIONS: Oral troglitazone therapy at various dosages in patients with psoriasis; also, use of troglitazone, ciglitazone, and 15-deoxy-delta-12,14-prostaglandinJ2 in psoriasis models. MAIN OUTCOME MEASURES: Investigator-determined clinical results in patients and cell counts and histological evidence in models. RESULTS: All patients' psoriasis improved substantially during troglitazone therapy. Peroxisome proliferator-activated receptor-gamma was expressed in human keratinocytes; ligands for PPARgamma inhibited the proliferation of normal and psoriatic human keratinocytes in culture. Troglitazone treatment normalized the histological features of psoriatic skin in organ culture and reduced the epidermal hyperplasia of psoriasis in the severe combined immunodeficient mouse and human skin transplant model of psoriasis ($P<.05$ compared with untreated controls). CONCLUSIONS: Peroxisome proliferator-activated receptor-gamma might be a useful intracellular target for the treatment of psoriasis; further study is needed to assess the clinical value of ligands for PPARgamma, including troglitazone.

Publication Types:
- Clinical Trial
- Controlled Clinical Trial

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1: Endocrinology 1999 Nov;140(11):5060-5

Thiazolidinediones inhibit osteoclast-like cell formation an bone resorption in vitro.

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Osteoblasts and adipocytes are derived from common bone marrow stromal cells that play crucial roles in the generation of osteoclasts. Activation of peroxisome proliferator-activated receptor-gamma (PPARgamma) induces adipogenic differentiation of stromal cells; however, whether this would affect osteoblast/osteoclast differentiation i unknown. Thus, we examined the effects of the thiazolidinedione (TZD) class of antidiabetic agents that activate PPARgamma on osteoblast/osteoclast differentiation using mouse whole bone marrow cell culture. As reported, all TZDs we tested (troglitazone, pioglitazone, and BRL 49653) markedly increased the number of Oil Red O-positive adipocytes and the expression of adipsin and PPARgamma 2. 1alpha,25-Dihydroxyvitamin D3 [1,25-(OH)2D3] did not affect adipogenic differentiation induced by TZDs. TZDs did not affect alkalin phosphatase activity, an early marker of osteoblastic differentiation, despite their marked adipogenic effects. TZDs decreased the number of tartrate-resistant acid phosphatase-positive multinucleated osteoclast-like cells induced by 1,25-(OH)2D3 or PTH. Troglitazone dose dependently inhibited basal and 1,25-(OH)2D3- and PTH-induced bone resorption as assessed by pit formation assay. Interleukin-11 blocked the induction by troglitazone of adipogenesis, but had no effect on the inhibition of osteoclast-like cell formation. These results indicate that TZDs are potent inhibitors of bone resorption in vitro. Inhibitory effects of TZDs on osteoclastic bone resorption was not osteotropic factor specific and did not appear to be related to their adipogenic effects. Thus, TZDs may suppress bone resorption in diabetic patients and prevent bone loss.

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